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January 14, 1999

BY HAND DELIVERY

Ms. Jane Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
Woodmont Office Complex 2
Room 6027 (HFD-5)
1451 Rockville Pike
Rockville, Maryland 20852

Re: Docket 98P-1075; Postmarketing Safety of Ticlopidine Hydrochloride

Dear Ms. Axelrad:

I am writing on behalf of Hoffmann-La Roche Inc. and Syntex (USA) Inc. (hereinafter referred to as "Roche") regarding the postmarketing safety of ticlopidine hydrochloride. Since the Food and Drug Administration ("FDA" or the "Agency") approved Roche's New Drug Application ("NDA") for TICLID® (ticlopidine hydrochloride tablets (250 mg)) ("Ticlid") in 1991, Roche has run an extensive postmarketing safety program for Ticlid, including complete blood count monitoring and patient and professional education. Currently, there are a number of pending abbreviated new drug applications ("ANDAs") and two tentative approvals of ANDAs for ticlopidine hydrochloride (250 mg) ("ticlopidine"). Following a lengthy dialogue with FDA on the topic, on November 27, 1998, Roche filed a Citizen Petition with FDA regarding the necessity of requiring a postmarketing safety program in connection with the sale and marketing of all forms of ticlopidine. The petition raises critical issues of drug safety and must be addressed prior to final approval of any ANDA for ticlopidine. 1/

1/ On January 11, 1999, Teva Pharmaceuticals USA, Inc. ("Teva") filed suit against FDA in the Federal District Court for the District of Columbia seeking declaratory and injunctive relief in connection with the approval and marketing of ticlopidine pursuant to an ANDA. Roche currently is not a party to this lawsuit but does plan to seek intervenor status.

As you know, drug safety is an issue of critical importance to the public, manufacturers, FDA and Congress. Postmarketing safety monitoring is one of FDA's primary tools to ensure the safe use of pharmaceutical products. Postmarketing programs make product use safer and help reduce adverse events. To the best of Roche's knowledge, to date FDA has "strongly encouraged" but not required generic manufacturers to provide postmarketing safety programs for generic ticlopidine. As requested in Roche's Citizen Petition, in order to ensure the continued safe use of ticlopidine FDA must require all ticlopidine manufacturers to adopt a postmarketing safety program. In its Citizen Petition Roche has offered two legal pathways to achieve this goal, including, if FDA concludes that such a postmarketing safety program is not already required of Roche, a commitment by the company to file a supplement to the Ticlid NDA to require a postmarketing safety program as a condition of use.

Roche's Citizen Petition was the culmination of nine months of dialogue with the Agency regarding whether FDA should require postmarketing safety programs of all manufacturers of ticlopidine. An important element of this dialogue was the commitment made by Roche to work with the ANDA applicants to develop comparable postmarketing safety programs. In October 1998, FDA wrote a letter to the ticlopidine ANDA applicants expressing the importance of and need for postmarketing safety programs. In addition, the Agency conveyed Roche's commitment to work with the applicants on developing postmarketing safety programs. Since that time only one of the approximately nine ANDA applicants has ever contacted Roche regarding the development of a postmarketing safety program. Further, the one company that did contact Roche, Purepac Pharmaceutical Co., placed one initial phone call, during which the parties discussed the nature of the available information and the possible exchange of the same and counsel for Purepac agreed to put this request in writing. That conversation took place weeks ago and Roche has never received any written follow up. Clearly, despite FDA's strong urging, it does not appear that the ANDA applicants will voluntarily implement postmarketing safety programs.

When FDA approved Ticlid in 1991, a black box warning regarding neutropenia was included in the product labeling. Due to the danger of neutropenia, FDA determined that a postmarketing safety program for Ticlid was

necessary. The Ticlid black box warning in the professional labeling and the PPI recently were revised to include the following statement as well as more detailed information on ticlopidine-associated TTP: "Ticlid can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP)." Given these important safety concerns associated with ticlopidine, the postmarketing safety program continues to provide invaluable safety information to patients and professionals, as well as continually reinforce the need for CBC monitoring, even if ticlopidine therapy is discontinued. Indeed, ticlopidine has never been marketed in the U.S. without a postmarketing safety program. Because the Ticlid postmarketing safety program is critical to the safe use of the product, the Agency should require the same postmarketing safety program of all manufacturers.

In light of the nine months of dialogue leading to the Citizen Petition, the importance of the postmarketing safety program, and the lack of responsiveness on the part of the ANDA applicants to FDA's request for the implementation of postmarketing safety programs, we believe it is critical that the Agency affirmatively address the concerns raised by the petition before issuing a final approval for any ticlopidine ANDA and require all ticlopidine manufacturers to adopt postmarketing safety programs. Accordingly, we hope that you will give this Citizen Petition and the important drug safety issues that it raises your attention and the serious consideration it warrants prior to issuing any final approvals.

Over the last several days I have attempted to speak with several CDER officials regarding the status of the Citizen Petition and the prospect for an Agency response prior to a final ANDA approval. All have respectfully declined to answer my questions. Accordingly, we hereby are requesting a meeting with you

and others you deem appropriate to discuss this issue. If you have any questions or if I can be of assistance, please do not hesitate to contact me.

Sincerely,

Robert P. Brady /mon

Robert P. Brady
Counsel for Hoffmann-La Roche Inc.

cc: Dr. Janet Woodcock - CDER/Director
Dr. Robert Temple - CDER
Dr. Raymond J. Lipicky - DCRDP
Dr. Robert Fenichel - DCRDP
Dr. Stephen Fredd - DCRDP
Mr. Douglas Sporn - OGD
Mr. Robert West - OGD
Mr. David Fox - OGC